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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/715,902	11/17/2000	John James Donnelly	1627.003	5612

27476 7590 12/18/2003

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/715,902	DONNELLY ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-23,29-31,33-44,46,50,52 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18-23,29-31,33-44,46,50,52 and 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/10/03 has been entered. As requested, the amendment filed on 9/9/03 has also been entered. Claims 17, 24-28, 32, 45, 47-49, and 51 have been canceled. Claims 1-16, 18-23, 29-31, 33-44, 46, 50, and 52-53 are currently pending and under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action, can be found in previous office actions.

Claim Rejections - 35 USC § 103

The rejection of pending claims 1-16, 18-23, 29-31, 33-44, 46, 50, and 52-53 under 35 U.S.C. 103(a) as being unpatentable over WO 97/24447, 7/10/97, hereafter referred to as Song et al., in view of US Patent No. 5,783,567 (7/21/98), hereafter referred to as Hedley et al., and further in view of Fattal et al. (1998) J. Controlled Rel., Vol. 53, 137-143, is maintained.

Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons of record as discussed in detail below.

The applicant argues that the prior art cited by the office does not provide sufficient motivation or a reasonable expectation of success for making /using applicant's claimed invention. In particular, the applicant states that motivation for combining the references only exists with the benefit of hindsight afforded by the present application. In response to applicant's arguments regarding hindsight reasoning, it is noted that "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." *In re McLaughlin*, 443 F2d. 1392, 170 USPQ 209, 212 (CCPA 1971). In addition, please note that it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Burkel*, 201 USPQ 67 (CCPA 1979). In the determination of obviousness, the state of the art as well as the level of skill of those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. Further, the test for combining references is not what the individual references themselves suggest, but rather what the combination of disclosures taken as a whole would have suggested to one of ordinary skill in the art. *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). For the purpose of combining

references, those references need not explicitly suggest combining teachings, much less specific references. *In re Nilssen*, 7 USPQ2d 1500 (Fed. Cir. 1988). Finally, please note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell*, 7 USPQ2d 1673 (CAFC 1988).

In response to applicant's arguments concerning each reference individually, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant's arguments regarding the teachings of each reference are addressed below in the context of the combined teachings of Song et al., Hedley et al., and Fattal et al.

The applicant acknowledges that Song et al. teaches several gene delivery vehicles for gene livery to dendritic cells, but argues that Song et al. does not teach a transfection agent comprising a polynucleotide and a microparticle as claimed, and that Song et al. demonstrates a preference for recombinant retroviral techniques over non-viral techniques. The applicant further argues that neither Hedley et al. nor Fattal et al. overcome this deficiency in Song.. As discussed in detail in the previous office actions, Song et al. teaches methods of transfecting dendritic cells *ex vivo* or *in vitro* with a gene delivery vehicle comprising DNA encoding an antigen such as a tumor antigen or HIV antigen, and use of said transfected dendritic cells to induce an immune response against the expressed antigen in vivo (Song et al., pages 2, 3, and 18-20). Regarding

gene delivery vehicles taught by Song et al., Song teaches that for *ex vivo/in vitro* transfection of dendritic cells, both non-viral and viral gene delivery vehicles can be used, including the use of expression vectors complexed with polycations or lipids or encapsulated in liposomes (Song et al., page 1, and pages 14-19). Thus, Song et al. teaches that numerous gene delivery vehicles can be successfully utilized to transfect dendritic cells including the use of plasmid/liposomes, and plasmid combined with cationic condensing agents. The fact that Song et al. exemplified retroviral transduction of dendritic cells does not invalidate the clear teachings in this reference that many techniques, including non-viral techniques, can be used to transfect dendritic cells *in vitro*.

In regards to the teachings of Hedley et al., the applicant argues that Hedley primarily teaches the use of microparticles to transfect macrophage and does not specifically teach *in vitro* transfection of dendritic cells. In response, Hedley et al. has been cited for the use of microspheres comprising biodegradable polymers and DNA plasmids to introduce and express antigens encoded by the plasmids in antigen presenting cells such as macrophages and dendritic cells both *in vitro* and *in vivo* for the purpose of stimulating antigen specific immune responses (Hedley et al., columns 2-3 and 7-8). Hedley et al. further provides motivation for introducing plasmid DNA encoding an antigen to dendritic cells and macrophages using biodegradable microspheres by teaching that DNA combined with biodegradable microparticles is efficiently phagocytosed by APCs and is an effective means for introducing nucleic acids into these cells (Hedley et al., column 8, lines 13-49). While Hedley exemplifies the transfection of macrophages, the teachings of Hedley et al. are not so limited. Hedley et al. clearly teaches the transfection of APCs, antigen

presenting cells. Dendritic cells were well known at the time of filing as antigen presenting cells, as evidenced by Song et al. Further, Hedley et al. recognizes that dendritic cells are a legitimate target for the microparticle transfection when they state that the point of introduction of plasmid/microparticles to skin is the transfection of dendritic cells. Motivation for transfecting dendritic *ex vivo/in vitro* is derived primarily from the teachings of the primary reference, Song et al., who clearly teaches the transfection of dendritic cells *ex vivo*, see above. However, Hedley et al. also teaches *ex vivo* transfection. In column 12, lines 23-30, Hedley et al. clearly states, "For in vitro/ex vivo use, the suspension of microparticles can be added either to cultured adherent mammalian cells or to a cell suspension". Thus, Hedley et al. clearly contemplates *ex vivo* transfection of APCs. Again, Song et al. already teaches the transfection of dendritic cells, Hedley is cited to provide motivation for using microparticles as a transfection agent.

The applicant's further argues that the successful transfection of macrophages exemplified by Hedley et al. does not provide a reasonable expectation of success for transfection of dendritic cells because dendritic cells are resistant to transfection using *ex vivo* nonviral techniques. In support of this argument, the applicant cites two post-filing publications by Denis-Mize et al. and Lundquist et al., which state that dendritic cells are not readily transfected by traditional non-viral techniques. With due respect to the teachings of Denis-Mize et al. and Lundquist et al., the prior art contains numerous successful examples of the transfection of dendritic cells *ex vivo/in vitro* using plasmid DNA, either alone or in combination with liposomes or even gold beads. In rebuttal to applicant's citation of Denis-Mize et al. and Lundquist et al., the office provides the following

evidence that in fact dendritic cells transfection using non-viral techniques was well known at the time of filing. Please note that the references cited below are not part of the rejection of record, but are simply provided to rebut applicant's arguments. Yang et al. teaches the successful transfection of dendritic cells *ex vivo* with plasmid DNA encoding gp100 in the presence of Lipofect-AMINE, and the successful use of the transfected dendritic cells to generate therapeutic anti-tumor immune responses after re-introduction of the cells into animals (Yang et al. (1999) Int. J. Cancer, Vol. 83, 532-540). Manickan et al. teaches the successful transfection of dendritic cells *ex vivo* with plasmid DNA encoding the gB or ICP-27 proteins of HSV-1 in the presence of DOTAP, and the successful use of these cells to induce anti-HSV immune responses *in vivo* (Manickan et al. (1997) J. Leuk. Biol., Vol. 61, 125-132). Spahn et al. teaches the successful transfection of dendritic cells *in vitro* with plasmid DNA encoding MUC1 and liposomes (Spahn et al. (1996) Proc. Am. Assoc. Canc. Res., Vol. 37, 486-487). Tuting et al. teaches the successful transfection of dendritic cells *in vitro* with plasmid DNA encoding tumor antigens coated onto gold beads (Tuting et al. (1998) J. Immunol., Vol. 160, 1139-1147). Thus, contrary to applicant's arguments, at the time of filing, the skilled artisan would have certainly had a reasonable expectation of success in transfecting dendritic using non-viral techniques.

The applicant further argues that the claims as amended now read on microparticles where the nucleic acid is absorbed onto the surface and that Hedley et al. teaches that the nucleic acid is encapsulated within the microparticles. In response, the claims as amended still encompass

microparticles with encapsulated nucleic acid, see in particular claims 46 and 50 which specifically recite wherein a portion of the polynucleotide is entrapped within said microparticles. Thus, the claims as amended read on microparticles which have polynucleotide absorbed to the surface and encapsulated within the particle. Further, the interaction of the polynucleotide with the microparticle depends on the charge characteristics of the microparticle itself and the presence or absence of additional molecules such as detergents or surfactants. The microparticles taught by Hedley et al. are not positively charged, thus combining the microparticles with the polynucleotide results in encapsulation. On the other hand, Fattal et al. clearly teaches that adding a cationic detergent to the biodegradable microparticles results in particles with a positive charge such that the majority of the negatively charged polynucleotide absorbs onto the cationic surface rather than encapsulating within. Fattal et al. provides a useful diagram of the interactions on page 139, Figure 1. Further, Fattal et al. was cited for providing motivation for using a cationic detergent such as CTAB in the preparation of transfection agents comprising biodegradable polymers and polynucleotides in order to increase the amount of polynucleotide associated with the polymer particles and increase the uptake of the nucleic acid by phagocytosis. In view of the motivation provided by Fattal et al., it would have been *prima facie* obvious to the skilled artisan at the time of filing to include a cationic detergent in gene delivery vehicle comprising biodegradable polymers in order to increase the association of polynucleotide with the particle and thus to increase phagocytosis of the nucleic acid by the target cell.

In regards to Fattal et al., the applicant argues that Fattal et al. teaches antisense oligonucleotide rather than plasmid DNA and as such there would be no reasonable expectation of success in making CTAB microparticles according to Fattal et al. using plasmid DNA. The office disagrees, Figure 1 of Fattal et al. clearly demonstrates the chemical interaction between the oligonucleotide and the cationic microparticle. According to Fattal et al., it is the negatively charged phosphate groups of the nucleic acid chain that form ion pairs with the hydrophobic cations on the surface of the biodegradable microparticles (Fattal et al., page 139, column 1). Regardless of whether the nucleic acid is "antisense" oligonucleotide or nucleic acid present in a DNA plasmid, the nature of nucleic acids is that the backbone of the molecule is negatively charged. Thus, based on the nature of the negatively charged phosphate groups present in all nucleic acids, the skilled artisan would have had reasonable expectation that negatively charged plasmid DNA would likewise form ion pairs with CTAB or another cationic detergent.

The applicant further argues that the skilled artisan would not be motivated to use cationic detergents with biodegradable microparticles because cationic detergents may impart stickiness to the resulting microparticles or have increased toxicity compared to nonionic detergents. However, since Fattal et al. actually teaches biodegradable microparticles with a cationic detergent and the use of the particles to deliver nucleic acid to cells, applicant's concerns about whether the skilled artisan would be motivated to combine a cationic detergent and a microparticle are moot. Fattal et al. already teaches just that combination. In fact, as noted in previous office actions, Fattal et al. provides clear motivation for including a cationic detergent in a microparticle by teaching that

inclusion of a cationic detergent in microparticles increases the amount of polynucleotide associated with the polymer particles and increases the uptake of the nucleic acid by phagocytosis.

Finally, the applicant argues that the claims as amended recite that the nucleic acid is exposed to microparticles comprising a biodegradable polymer and a cationic detergent and that Fattal teaches admixing oligonucleotide with detergent prior to exposure to nanoparticles. The Office disagrees with applicant's description of Fattal et al. On page 138, Fattal et al. clearly teaches that the oligonucleotide is added to a suspension comprising microparticles and CTAB (Fattal et al., page 138, column 2, paragraph 2).

Thus, for the reasons discussed above, applicant's arguments and supporting evidence have not been found persuasive in overcoming the instant grounds of rejection of the claims as written.

Claim Objections

Claims 52-53 are objected to under 37 CFR 1.75(c), as being in improper form because a multiple dependent claim must refer to the parent claims in the alternative. See MPEP § 608.01(n). Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 872-9306.

Please note that the United States Patent and Trademark Office will begin to move to the new campus in Alexandria, Virginia, in December 2003. The examiners of Art Unit 1632 will be moving in January 2004. As of January 13, 2004, this examiner's phone number will be (571) 272-0737, and that of the examiner's supervisor will be (571) 272-0734.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER